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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/623,038	11/27/2000	George M. Carlone	65446	5598

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NEEDLE & ROSENBERG, P.C.
SUITE 1000
999 PEACHTREE STREET
ATLANTA, GA 30309-3915

EXAMINER	
DEVI, SARVAMANGALA J N	
ART UNIT	PAPER NUMBER
1645	

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14

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/623,038	Carlone et al.
Examiner	**Art Unit**
S. Devi, Ph.D.	1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jun 12, 2003*.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above, claim(s) *7, 13, 14, 17, 19, 21, and 22* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-6, 8-12, 15, 16, 18, and 20* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☒ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *9.*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Sequence alignment report.*

DETAILED ACTION

Preliminary Amendment

1) Acknowledgment is made of Applicants' amendment filed 07/16/02 (paper no. 8).

Election

2) Acknowledgment is made Applicants' election filed 06/12/03 (paper no. 13) in response to the written lack of unity mailed 05/12/03 (paper no. 12). Applicants have elected with traverse invention II, claims 6, 12, 15, 16, 18 and 20, drawn to a peptide of SEQ ID NO: 6 or a fragment thereof. Applicants' traversal is on the grounds that if a group of inventions is claimed in a single application, there must be a technical relationship between inventions involving one or more of the same or corresponding special technical features. Applicants state that 'Special technical features' shall mean those technical features which define a contribution which each of the claimed inventions, claimed as a whole, makes over the prior art. Applicants assert that the claims of the present invention are directed to a composition comprising a peptide, or the peptide, or a method of using the composition/peptide. Applicants state that these claims fall into 37 C.F.R 1.475(b)3 -a product, a process specially adapted for the manufacture of said product and use of said product. Applicants opine that for this reason the claims should be considered to have unity of invention. Applicants allege that the special technical feature unifying the claims has been defined by the Office too narrowly, i.e., by the specific species listed, for example, in claim 6. Applicants urge that the special technical feature is 'a peptide that immunospecifically binds to a monoclonal antibody obtained in response to immunizing an animal with *S. pneumoniae* PsaA'. Applicants allege that the special technical feature in this case 'cannot be defined so narrowly' to be any one of the four peptides or a fragment thereof. Applicants further allege that Pinchersky (US 5,849,526) does not disclose a sequence of six amino acids, but a sequence of 870 amino acids. Applicants then take another position and insist that the proper comparison to the prior art for the peptide species is a peptide described in claim 1, i.e., a peptide that immunospecifically binds to a monoclonal antibody obtained in response to immunizing an animal with *S. pneumoniae* PsaA comprising residues whose sequence is chosen from the group consisting of SEQ ID NO: 6, 6, 7, 8 or a fragment thereof. Applicants further allege that there is no assertion that the prior art 6-amino acid sequence is indeed long enough to be antigenic. Applicants ask that the Office's '10 Sequence Rule' should apply in the

present restriction. Applicants state that the Office's 'rule' MPEP 803.04 states that the Office will normally search up to 10 unrelated sequences in a single application. Applicants then mix the lack of unity issue with the requirements under the US restriction practice and conclude that a search for a given sequence/fragment in one class/subclass would also turn up relevant patents for all of the groups in the same class/subclass. Applicants also contend that a search relating to a peptide that immunospecifically binds to a monoclonal antibody obtained in response to immunizing an animal with *Streptococcus pneumoniae* PsaA would necessarily be a search for each of the listed SEQ ID in the dependent claims.

Applicants' arguments have been carefully considered, but are non-persuasive. The Office Action mailed 05/12/03 (paper no. 12) is a lack of unity under PCT Rule 13.1 and 13.2 as opposed to a restriction requirement under 35 U.S.C. 121. Most of Applicants' arguments are unrelated to the lack of unity set forth in the Office Action mailed 05/12/03 (paper no. 12). Arguendo, even if one considered the broadly recited peptide of claim 1 to be the special technical feature, which peptide immunospecifically binds to a monoclonal antibody obtained in response to immunizing an animal with *S. pneumoniae* PsaA, even then, the special technical feature is not a unifying feature, because it was already disclosed in the prior art. As is clear from the art rejections made below, several skilled in the art other than Pinchersky have also disclosed the peptide that is being claimed in claim 1. The patent issued to Sampson *et al.* (US 6,217,884) taught the peptide claimed in claim 1. This is *prima facie* evidence that the special technical feature identified by Applicants does not define over the prior art. According to PCT Rule 13.2, if an independent claim does not avoid the prior art, an inventive link between all the claims dependent on the independent claim is to be considered lacking. In the instant application, the different recognized inventions are not so linked as to form a single general inventive concept as a technical relationship involving one or more of the same, or corresponding special technical features in the sense of Rule 13.2 PCT does not exist between the subject matter of the different recognized inventions. Therefore, since the special technical feature does not define over the prior art, the special technical feature is not a unifying feature. Technically, this absence of special technical feature would permit the separation of method of using or making the product from the product itself. Further, it should be noted that the various sequences recited in claim 6, for example, do not share significant structural elements and each requires a separate

structural search. A structural sequence search performed for one SEQ ID number would not necessarily yield all the relevant prior art for the rest of the SEQ ID numbers. The lack of unity set forth in the Office Action mailed 05/12/03 (paper no. 12) is proper and is hereby made FINAL.

Status of Claims

3) Claims 1-22 are pending.

Claims 7, 13, 14, 17, 19, 21 and 22 have been withdrawn from consideration as being directed to a non-elected invention. See 37 C.F.R 1.142(b) and M.P.E.P § 821.03.

Elected claims 6, 12, 15, 16, 18 and 20 to the extent these claims encompass SEQ ID NO: 6, and linking claims 1-5 and 8-11 are under examination.

Sequence Listing

4) Acknowledgment is made Applicants' submission of the CRF and the Sequence Listing. The CRF error, i.e., non-ASCII 'garbage' at the beginning/end of the file has been corrected by the STIC Systems Branch and the Sequence Listing has been entered.

Priority

5) The instant application is a national stage 371 application of PCT/US99/04326, filed 02/26/1999 and claims domestic priority to application 60/076,565 filed 03/02/1998.

Information Disclosure Statements

6) Acknowledgment is made of Applicants' Information Disclosure Statements filed 03/15/02 (paper no. 6) and 07/22/02 (paper no. 9). The documents referred to have been considered. A signed copy is attached to this Office Action (paper no. 14).

Sequence Rule Non-compliance

7) The specification at line 20 on page 36 and line 31 on page 37 appears to recite an amino acid sequence that is longer than four residues in length, yet is not identified, by a SEQ ID number as required under 37 C.F.R 1.821 through 1.825. Any sequences recited in the instant specification which are encompassed by the definitions for nucleotide and/or amino acid sequences as set forth in 37 C.F.R. 1.821(a)(1) and (a)(2) must comply with the requirements of 37 C.F.R 1.821 through 1.825. All SEQ ID numbers recited in the specification and/or the claims must be included in the Sequence Listing. Note that branched sequences are specifically excluded from this definition. Applicants must submit a substitute paper copy of the Sequence Listing and an amendment directing

its entry at the appropriate section of the specification.

APPLICANT MUST COMPLY WITH THE SEQUENCE RULES WITHIN THE SAME TIME PERIOD AS IS GIVEN FOR RESPONSE TO THIS ACTION, 37 C.F.R 1.821 - 1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 C.F.R 1.821(g).

Abstract

8) The abstract of the disclosure is objected to because the number of words contained in the abstract exceeds the number of words permitted. Correction is required. See MPEP § 608.01(b).

Specification - Informalities

9) The specification is objected to for the following reason(s):

(a) The first paragraph of the specification lacks the priority information as indicated above under the section 'Priority'. Amendments to the first paragraph of the specification is suggested.

(b) The use of the trademarks in the instant specification has been noted in this application. For example, see line 27 on page 42: 'Sequenase'; line 17 on page 26: 'Triton X-100' and 'Tween ...'; and lines 11 and 13 on page 24: 'Tween-20'. Although the use of trademarks is permissible in patent applications, the propriety nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks. It is suggested that Applicants examine the whole specification and make necessary changes wherever trademark recitations appear.

Rejection(s) under 35 U.S.C § 101

10) 35 U.S.C. § 101 states:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this cycle.

11) Claims 1, 15 and those dependent therefrom are rejected under 35 U.S.C. § 101 because the claimed invention is directed to non-statutory subject matter.

Claims 1 and 15, as written, do not sufficiently distinguish over peptides as they exist naturally because the claims do not particularly point out any non-naturally occurring differences between the claimed products and the naturally occurring products. In the absence of the hand of

man, the naturally occurring products are considered non-statutory subject matter. See *Diamond v. Chakrabarty, 447 U.S. 303, 206 USPQ 193 (1980)*. The claim(s) should be amended to indicate the hand of the inventor, e.g., by insertion of 'Isolated" or "Purified" or "Isolated and purified" as is taught in the specification. See MPEP 2105.

Rejection(s) under 35 U.S.C. § 112, First Paragraph

12) Claim 2 is rejected under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure, because the specification does not provide evidence that the claimed biological material is (1) known and readily available to the public; (2) reproducible from the written description, e.g. sequenced; or (3) deposited.

Claim 2 is directed to a pneumococcal peptide that immunospecifically binds to a specific monoclonal antibody: 1B6E12H9; 3C4D5C7; 4E9G9D3; 4H5C10F3; 6F6F9C8; 8G12G11B10; and 1E7A3D7C2. It is apparent that these monoclonal antibodies are required to practice the claimed invention. As required elements, the monoclonal antibodies must be known and be readily available to the public, or obtainable by a reproducible method set forth in the specification, or otherwise be readily available to the public. If the antibodies are not so obtainable or available, the enablement requirements of 35 U.S.C. § 112, first paragraph, may be satisfied by a deposit of the hybridoma producing the monoclonal antibodies.

From the specification on pages 12, 19, 27 and 40, it does not appear that the hybridoma producing the monoclonal antibodies recited as 1B6E12H9; 3C4D5C7; 4E9G9D3; 4H5C10F3; 6F6F9C8; 8G12G11B10; and 1E7A3D7C2 are deposited at a recognized depository. The monoclonal antibodies do not appear to be readily available to the public and it is unclear if the cell line can be reproducibly isolated without undue experimentation. Since obtaining such a monoclonal antibody with the exact specificity for the peptide is non-predictable, undue experimentation would be required to practice the invention. Without a publicly available deposit of the hybridoma cell lines, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: 1) a cell line; and 2) the cell line which produces the chemically and functionally distinct antibody is an unpredictable event. Deposit of the hybridoma producing the recited monoclonal antibodies would satisfy the requirements of 35 U.S.C. § 112, first paragraph.

If a deposit has already been made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by Applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposit will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed by the depository is required. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each state. The specification should be amended to include complete deposit information for the hybridoma producing the recited antibodies, including the full address of the depository and the date of deposition. Additionally, Applicants are requested to amend the specification and the claim(s) with the proper information regarding the depository number and provide evidence to support the insertion for the depository number. The recitation of a laboratory designation does not clearly define the recited monoclonal antibodies. Amending the claim to include the cell line deposit numbers following the laboratory designations is suggested.

Applicants' attention is directed to *In re Lundack*, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 C.F.R § 1.801-1.809 for further information concerning deposit practice.

13) Claims 6, 12, 15, 16, 18 and 20 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection. The claims are viewed as not providing sufficient written description under 35 U.S.C § 112, first paragraph, for one to practice the invention.

One or more of the instant claims encompass a peptide having "at least 80% identical to a peptide whose sequence is SEQ ID NO: 6 or an immunogenic fragment thereof", or 'a fragment of SEQ ID NO: 6'. The specification intends therapeutic and diagnostic applications for the peptide, peptide fragment or the at least 80% identical peptide variant. The peptides claimed in claims 12, 16, 18 and 20 are required to confer 'protective immunity against *S. pneumoniae*' infection. However, the specification, as originally filed, does not provide adequate written description that would allow

one skilled in the art to obtain a peptide having at least 80% sequence identity to the peptide of SEQ ID NO: 6 and concurrently having the immunogenic and/or the protective ability against *S. pneumoniae*. There is no evidence within the instant specification describing how to obtain a peptide fragment, or a peptide variant having at least 80% identity to SEQ ID NO: 6, or a fragment thereof having the recited functional properties of immunogenicity and/or protective ability. With regard to the claimed peptide "fragment", neither the structural characteristics nor the functional or biological characteristics of the claimed peptide fragment are disclosed. There is lack of written description as to which specific fragment of the peptide of the amino acid sequence of SEQ ID NO: 6 is encompassed in the claimed peptide fragment. The specification lacks written description as to whether retention of any fragment from any part of the 15 amino acid-long peptide of SEQ ID NO: 6 (i.e., terminal or central parts) would yield a peptide fragment that would have the expected biologic, i.e., immunogenic and/or protective functions. Adequate written description is critical since the art reflects sensitivity of proteins to alterations of even a single amino acid in a sequence. For instance, Burgess *et al* (*J. Cell Biol.* 111: 2129-2138, 1990) teach that replacement of a single lysine residue at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. Similar teachings are provided by Lazar *et al* (*Mol. Cellular Biol.* 1988, 8: 1247-1252) who show that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity, while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. Therefore, without a precise written description of the specific amino acid residues contained within the claimed peptide variant or a fragment thereof, one of ordinary skill in the art cannot be sure of the sequences embraced by the claims and would not be able to make and use those protein sequences or fragments as recited in the instant claims, without undue experimentation. One of ordinary skill in the art would not be able to make and use such peptide fragments or variants, for example, as a component of a therapeutic composition, without undue experimentation.

Vas-Cath Inc. V. Mathukar, 19 USPQ2d 1111 states that Applicant "must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention, is for purposes of the 'written description' inquiry,

whatever is now claimed." See page 1117. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." See page 1116 of *Vas-Cath Inc. V. Mathukar, 19 USPQ2d 1111*. Applicants should also note that *Vas-Cath Inc. V. Mathukar, 19 USPQ2d 1111* makes clear that the written description provision of 35 U.S.C § 112, first paragraph, is severable from its enablement provision. See page 1115. Irrespective of the simplicity or complexity of the isolation method, conception is not achieved until reduction to practice has occurred. Adequate written description requires more than a mere statement that it is part of the invention. The claimed product having the recited percent identity and/or function(s) itself is required. Therefore, the claims are viewed as not meeting the written description provision of 35 U.S.C § 112, first paragraph.

14) Claims 6, 12, 15, 16, 18 and 20 are rejected under 35 U.S.C § 112, first paragraph, because the specification, while being enabling for a composition comprising a 37-kDa protein of *S. pneumoniae* that confers protective immunity against challenge with a wild-type *S. pneumniae*, does not reasonably provide enablement for a peptide of SEQ ID NO: 6, a fragment thereof, or a variant thereof having at least 80% sequence identity to SEQ ID NO: 6 which is immunogenic and/or is able to confer protective immunity against challenge with a wild-type *S. pneumoniae*, as claimed. The specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with the claims.

The instant claims are evaluated based on the *Wands* analysis. Many of the factors regarding undue experimentation have been summarized in *In re Wands, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Circ. 1988)* as follows:

- The quantity of experimentation necessary (time and expense);
- The amount of direction or guidance presented;
- The presence or absence of working examples of the invention;
- The nature of the invention;
- The state of the art;
- The relative skill of those in the art;
- The predictability or unpredictability of the art; and
- The breadth of the claims.

In the instant case, the claimed one or more peptides, the peptide fragment and the peptide variant having at least 80% sequence identity to the peptide of SEQ ID NO: 6 are required to be

immunogenic and/or are protective against *S. pneumoniae* for use in a therapeutic composition. The peptide, a fragment or variant thereof as recited is intended for inducing a protective immune response to *S. pneumoniae* in a subject. Although a microbial polypeptide or protein is expected in the art to generally induce specific antibodies, the ability of peptides, undefined "fragments" or peptide variants having at least 80% sequence identity to the peptide of SEQ ID NO: 6 to confer protective immunity against a microbial disease, pneumonia in the instant case, or to serve as a specific diagnostic reagent, is not predictable. The instant specification fails to teach how to produce a peptide "fragment", or a peptide having at least 80% sequence identity to the peptide of SEQ ID NO: 6 such that it is capable of serving as a therapeutic composition and capable of conferring protective immunity to *S. pneumoniae* infection in a human or non-human subject. The specification provides no guidance as to which specific amino acids must be retained in a "fragment" or which may be varied in the peptide of SEQ ID NO: 6 without causing any detrimental effect to the claimed peptide that is meant to induce a protective immune response in a subject against *S. pneumoniae* infection. There is no guidance in the instant specification with regard to which amino acid variations, i.e., insertions, deletions, additions and substitutions, in the peptide would result in a peptide fragment or variant that would retain the functional integrity or biological/immunogenic competence of the native protein, without rendering it non-functional. There appears to be no evidence within the instant specification, as originally filed, showing that the peptide of SEQ ID NO: 6, or fragment or a variant thereof having 80% sequence identity to the peptide of SEQ ID NO: 6 is capable of conferring protective immunity against *S. pneumoniae*. There appears to be not even a showing that the unmodified 15 amino acid-long peptide of SEQ ID NO: 6, let alone its fragment or variant having at least 80% sequence identity, does indeed confer protective immunity against *S. pneumoniae*. A review of the specification suggests that the 'Results' section on page 31 and Example 4 of the specification describe the protective ability of the 37-kDa protein of *S. pneumoniae*. Table 4 shows that the peptide of SEQ ID NO: 6 is 1B6 mAb-specific. Example 14 shows that the peptide of SEQ ID NO: 6 when conjugated to KLH and mixed with an adjuvant is immunogenic in mice. The protection experiments described in Examples 4 and 5 are limited to a showing that the whole 37-kDa protein of *S. pneumoniae* confers protection in mice against challenge with a wild-type *S. pneumoniae*. The specific monoclonal antibodies recited in the claims

were generated using the 37-kDa protein. However, there is no showing that the peptide of SEQ ID NO: 6, a fragment thereof, or a variant thereof having at least 20% dissimilarity to SEQ ID NO: 6 is protective against *S. pneumoniae*. The immunogenicity of a fragment of the peptide of SEQ ID NO: 6 or a variant of the peptide of SEQ ID NO: 6 as recited is not established. This is important because the art reflects unpredictability as to which amino acids in a specific protein can be varied, i.e., replaced or added, without adversely affecting the functional properties of that specific protein. While it is known in the art that variation in one or more amino acids is possible in a given protein, the exact position within its amino acid sequence where replacements or variations can be made, with a reasonable expectation of success of retaining the protein's functional integrity, is not certain. A random replacement affecting the epitopic amino acid positions that are critical, for example, to the three-dimensional conformational structure and specific binding property of the protein, would result in a polypeptide that may be non-functional (i.e., non-immunogenic) or not optimally immunogenic or protective as a vaccine candidate, because such positions tolerate no or little modifications. For instance, Houghten *et al.* (New Approaches to Immunization, *Vaccines86*, Cold Spring Harbor Laboratory, p. 21-25, 1986) teach the criticality of individual amino acid residues and their positions in peptide antigen-antibody interactions. Houghten *et al.* state (see page 24):

> One could expect point mutations in the protein antigen to cause varying degrees of loss of protection, depending on the relative importance of the binding interaction of the altered residue. A protein having multiple antigenic sites, multiple point mutations, or accumulated point mutations at key residues could create a new antigen that is precipitously or progressively unrecognizable by any of the antibodies in the polyclonal pool.

Thus, the art reflects that variations in critical residues at specific positions in an amino acid sequence could result in a polypeptide which may induce an antibody that may not recognize or bind to the native polypeptide of a microorganism. In the instant case, this is important because one of the purposes of the instant invention is to produce a peptide of *S. pneumoniae* in its biologically active, immunogenic and/or protective form for inducing a protective immune response. The instant disclosure lacks guidance on the precise position(s), nature and extent of amino acid replacements or variations that can be made in the claimed peptide in order to produce a 'fragment' or a variant with 80% identity to SEQ ID NO: 6, and with regard to whether it would serve as an effective immunogen capable of conferring protective immunity against *S. pneumoniae* infection in a human or a non-human subject.

Therefore, undue experimentation would have been required to reproducibly practice the full scope of the invention as claimed currently, due to the lack of adequate and specific guidance, the lack of evidentiary support in the specification enabling a functional "fragment" peptide or a variant peptide having at least 80% sequence identity to SEQ ID NO: 6, the nature of the invention, the state of the prior art, the quantity of experimentation necessary and the art-demonstrated unpredictability in determining amino acid variations that are acceptable. *Ex parte Foreman, 230 USPQ 546, 547 (Bd. Pat. Appls. And Interf. 1986)*. One of ordinary skill in the art would not have been able to make a peptide fragment or a variant of the claimed peptide and use it, for example, for inducing anti-pneumococcal protective immune response in any subject, without undue experimentation, because there is no disclosure as to what positions and what specific amino acid residues are varied or truncated. The production and use of a fragment or variant of the peptide of SEQ ID NO: 6 that is capable of inducing a protective immune response against pneumococcal infection(s) is well outside the realm of routine experimentation. The claims are viewed as not meeting the scope of enablement provisions of 35 U.S.C § 112, first paragraph.

Rejection(s) under 35 U.S.C § 112, Second Paragraph

15) Claims 1-6, 8-12, 15, 16, 18 and 20 are rejected under 35 U.S.C § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) Claims 6, 2, 15 and 20 are vague and indefinite in the recitation: "fragment", because it is unclear what is encompassed in this recitation. What constitutes a 'fragment', and how much of the peptide's original structure has to be retained such that the resulting product can be considered as a 'fragment', is not clear. The metes and bounds of the structure encompassed in the limitation 'fragment' is indeterminate. Does a single amino acid, or a dipeptide qualify as a 'fragment'?

(b) Claims 1, 8, 12 and 20 are vague and indefinite in the use of abbreviated limitations in the claim language: 'PsaA'. It is suggested that the abbreviation be recited as a full terminology at first occurrence, with its abbreviated recitation retained in parentheses.

(c) Claim 15 is vague in the recitation "peptide comprising a sequence ..... SEQ ID NO: .." without reciting that the sequence is an amino acid sequence. In order to distinctly claim the subject matter of the instant invention, it is suggested that Applicants replace the recitation with --

peptide comprising an amino acid sequence .....SEQ ID NO: ...--.

(d) Claims 6 and 15 are vague in the recitation "comprising residues whose sequence ..... SEQ ID NO: .." without reciting that the sequence is an amino acid sequence. In order to distinctly claim the subject matter of the instant invention, it is suggested that Applicants replace the recitation with --comprising residues whose amino acid sequence .....SEQ ID NO: ...--.

(e) Claims 12 and 20 are vague in the recitation "comprising residues whose sequences ..... SEQ ID NO: ...." without reciting that the sequence is an amino acid sequence. In order to distinctly claim the subject matter of the instant invention, it is suggested that Applicants replace the recitation with --comprising residues whose amino acid sequences ... SEQ ID NO..--.

(f) Claims 2-5, 9-11, 16 and 18, which depend directly or indirectly from claim 1, 6 or 15, are also rejected as being indefinite because of the vagueness or indefiniteness identified above in the base claim(s).

Rejection(s) under Double Patenting

16) The non-statutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970) and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 C.F.R 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 C.F.R 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 C.F.R 3.73(b).

Instant claims 1-6, 12, 15, 16, 18 and 20 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 1, 2, 8 and 12-14 of the application SN 09/613,092. Although the conflicting claims are not identical, they are not patentably

distinct from each other because of their overlapping scope. The above-identified claims of the co-pending application, with regard to the peptide of SEQ ID NO: 10 claimed therein, fall within the scope of the peptide having 80% identity to SEQ ID NO: 6 or an immunogenic fragment thereof, claimed in the instant claims.

This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

Rejection(s) under 35 U.S.C § 102

17) The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> **(b)** the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> **(e)** the invention was described in-
> **(2)** a patent granted on an application for patent by another filed in the United States before the invention by the Applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

18) Claims 1-5 and 8-11 are rejected under 35 U.S.C § 102(e) as being anticipated by Sampson *et al.* (US 6,217,884).

Sampson *et al.* disclosed a fragment (i.e., peptide) of a 37 kDa protein of *S. pneumoniae* which is used as a vaccine component as well as a reagent for identifying host antibodies raised against *S. pneumoniae* during infection. The specific monoclonal antibodies used are 1E7A3D7C2; 1B6E12H9; 3C4D5C7; 4E9G9C3; 4H5C10F3; and 6F6F9C8; and 8G12G11B10 (see abstract; and column 7, lines 40-46; all of columns 11 and 12 including the paragraph bridging columns 11 and 12; and column 13, lines 1-46). The composition comprises a unique fragment (i.e., a peptide) of the 37-kDa pneumococcal surface adhesion protein (i.e., PsaA) for use in inoculating a host such that the polypeptide fragment generates an active immune response in the host which protects the host from infection (see column 13, seventh full paragraph). The composition comprises a pharmaceutically acceptable carrier and adjuvants (see column 14, lines 1-24). Synthetic peptides disclosed include shorter and larger peptides (see last paragraph in column 10) or partial polypeptides (see first full paragraph). The immunoreactive fragment of the 37 kDa pneumococcal surface adhesin protein is at least about 6 consecutive amino acids (i.e., inclusive of 10-15, 12-22 or 15 amino acid residues in length) having the ability to evoke an immune response (see lines 52-59 in column 11). The

fragments are produced by selected modifications provided the immunogenicity of the peptide is not significantly impaired compared to the 37 kDa pneumococcal surface adhesin protein (see paragraph bridging columns 11).

Claims 1-5 and 8-11 are anticipated by Sampson *et al.*

19) Claims 1, 6 and 15 are rejected under 35 U.S.C § 102(b) as being anticipated by Nuijens *et al.* (WO 9117258) as evidenced by Harlow *et al.* (*In*: *Antibodies*: *A laboratory Manual*. Cold Spring Harbor Laboratory, Chapter 5, p. 76, 1988).

It is noted that claims 1, 2 and 6 do not place a limit on the size or length of the peptide claimed.

Nuijens *et al.* disclosed a therapeutic or prophylactic composition comprising a peptide having the sequence, SYQHDL, which shows 100% (i.e., at least 80%) sequence identity with a fragment of the instantly claimed peptide of SEQ ID NO: 6. See the attached sequence alignment; and Example II of Nuijens *et al.* The peptide is conjugated to a suitable carrier to enhance elicitation of an antibody response. Although Nuijens *et al.* are silent about the binding of the peptide to a monoclonal antibody obtained in response to immunizing an animal with *S. pneumoniae* PsaA as recited in claim 1, the prior art peptide sequence is viewed as the same as the Applicants' claimed peptide. The Office's position that Nuijens' peptide is the same as the Applicants' peptide is based upon the fact that every characteristic overlapping in Nuijens' and Applicants' disclosure are the same. In spite of the fact that Nuijens *et al.* are silent about the binding of the peptide to a monoclonal antibody obtained in response to immunizing an animal with *S. pneumoniae* PsaA, since the prior art peptide is structurally the same as the instantly claimed peptide, the peptide is expected to bind immunospecifically to the Applicants' monoclonal antibody which was inaccessible to Nuijens *et al.* at that time. The property of binding to the specific monoclonal antibody recited by the Applicants is viewed as inherent to the peptide of Nuijens *et al.* Due to the region of 100% sequence identity, the peptide of the prior art is expected to bind immunospecifically to a monoclonal antibody as recited, because the art recognizes that the smallest peptides which elicit antibodies that bind to the original full length protein are 6 amino acids in length. See the first sentence under 'Size of the Peptide' on page 76 of Harlow *et al.* The Office's position that Nuijens' peptide is the same as the Applicants' peptide is based upon the fact that every characteristic overlapping in Nuijens' and

Applicants' disclosure are the same. In spite of the fact that Nuijens *et al.* fail to teach all of Applicants' disclosed functional characteristics, there is sufficient overlap to reasonably conclude that Nuijens' peptide is one and the same as the Applicants' peptide. Since the prior art peptide is viewed as structurally the same as the instantly claimed peptide, it is expected to have the same properties as that of the instantly claimed peptide.

The teachings of Nuijens *et al.* anticipate the instant claims. Harlow *et al.* is **not** used as a secondary reference in combination with Nuijens *et al.*, but rather is used to show that every element of the claimed subject matter is disclosed by Nuijens *et al.* with the unrecited limitation(s) being inherent in view of what is known in the art as explained above. See *In re Samour* 197 USPQ 1 (CCPA 1978).

Objection(s)

20) Claims 6, 12, 15 and 20 are objected to for including non-elected subject matter.

Remarks

21) Claims 1-6, 8-12, 15, 16, 18 and 20 stand rejected.

22) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center located in Crystal Mall 1. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The CM1 facsimile center receives facsimile transmissions 24 hours a day and 7 days a week. The RightFax number for submission of before-final amendments is (703) 872-9306. The RightFax number for submission of after-final amendments is (703) 872-9307.

23) Any inquiry concerning this communication or earlier communication(s) from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (703) 308-9347. A message may be left on the Examiner's voice mail service. The Examiner can normally be reached on Monday to Friday from 7.15 a.m to 4.15 p.m. except one day each bi-week which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

August, 2003

S. DEVI, PH.D.
PRIMARY EXAMINER

SEQ ID NO. 6

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RESULT 6
AAR14929
ID   AAR14929 standard; Protein; 12 AA.
XX
AC   AAR14929;
XX
DT   13-FEB-1992  (first entry)
XX
DE   OT-2 antibody binding peptide (2).
XX
KW   Monoclonal antibody; antigen; immunogen; Factor XII; epitope.
XX
OS   Synthetic.
XX
PN   WO9117258-A.
XX
PD   14-NOV-1991.
XX
PF   01-MAY-1991;   91WO-US02990.
XX
PR   10-MAY-1990;   90US-0521820.
XX
PA   (CETU ) CETUS CORP.
XX
PI   Nuijens JH,  Huijbregts CCM,  Hack CE;
XX
DR   WPI; 1991-353779/48.
XX
PT   Treatment of sepsis using inhibitor of factor XII activation -
PT   comprises use of new OT-2 antibody
XX
PS   Claim 15,17; Page 24; 32pp; English.
XX
CC   Based on the known amino acid sequence of Factor XII, peptides
CC   corresp. to neutralising epitopes of the mol. are synthesised and
CC   used as immunogens to produce antibody.  The pref. peptides are
CC   represented in AAR14928-30.  Amino acid Asp in this sequence =
CC   residue 442.
XX
SQ   Sequence   12 AA;

  Query Match          40.0%;  Score 6;  DB 12;  Length 12;
  Best Local Similarity  100.0%;  Pred. No. 4.1;
  Matches    6;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy       2 SYQHDL 7
           ||||||
Db       5 SYQHDL 10
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